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PATENT

Attorney Docket No. 016243-000150

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
Richard H. Tullis	Examiner: J. Martinell
Serial No.: 08/078,~~767~~ 768	Art Unit: 1805
Filed: June 16, 1993	PROPOSED AMENDMENT
For: OLIGONUCLEOTIDE THERAPEUTIC AGENT AND METHODS OF MAKING SAME	**DRAFT: March 8, 1995**

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

In anticipation of an Examiner's Interview on March 13, 1995, Applicant submits a proposed response to the Final Office Action mailed November 28, 1994. Applicants respectfully request that the Examiner review the proposed response and accompanying Rule 132 Declarations to facilitate the discussion during the interview.

REMARKS

This invention is a novel means for selectively controlling the expression of a target protein in a cell by the binding of a sequence-specific oligonucleotide to a coding region of the corresponding mRNA. At the time of conception, this invention reflected a dramatic break with the conventional wisdom. Although others had explored the use of oligonucleotides to repress gene expression, the art taught that the *coding* regions of mRNA should be avoided due to the belief that the extensive secondary structure of the mRNA coding region would prevent efficient binding. The subject invention represented a significant

advance in the art. Applicant gratefully acknowledges the Examiner's withdrawal of the prior art rejections.

Applicant acknowledges that consideration of Rule 132 Declarations after mailing of a final Office Action is discretionary. Applicant asks that the Examiner consider them as timely filed. The underlying prosecution has been complex with rejections having multiple bases raised. In good faith, Applicant believed that the legal argument presented earlier fully addressed the rejection relating to enablement under §112. In that argument, Applicant explained that the Examiner's concern over *in vivo* stability of nucleic acids was not controlling because the concern was not related to the inventive principle being claimed. In the declarations submitted herewith, Applicant seeks to document, through published articles, that other modified oligonucleotides were available as of the filing date of the invention in October of 1981 and that the *in vivo* stability of unmodified oligonucleotides is sufficient to permit practice of the invention.

STATUS OF THE CLAIMS

Claims 64-72 are pending. The claims stand rejected under 35 U.S.C. §112, first paragraph.

REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

The Examiner has maintained a single rejection of the claims under 35 USC §112, first paragraph, alleging that the disclosure is enabling only for claims limited to the preparation and uses of phosphotriester-modified oligodeoxyribonucleotides. The Examiner has asserted that "[the] instant application does not give one of skill in the art the guidance in connection with other forms of oligodeoxyribonucleotides that would be stable *in vivo*." (Office Action mailed on April 1, 1992, at page 2, third full paragraph[1]). In the previously

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1 Applicant understands the "reasons already of record" referred to in the November 28 Office Action to be those at page 2, third full paragraph, of the Office Action mailed April 1, 1992.

submitted Amendment, Applicant argued that the Examiner's §112 rejection was misplaced because the use of phosphotriester-modified oligonucleotides is not the inventive principle of the claimed method. The Examiner rejected this argument because he questioned the stability *in vivo* of phosphodiester oligodeoxyribonucleotides (hereinafter, "oligo-DNAs"), suggesting that the claimed invention would not work when oligo-DNAs are used. Based on the alleged inoperability of the invention when oligo-DNAs are used, the Examiner concluded that the claims should be limited to only the exemplified embodiment.

Applicant respectfully traverses this rejection with several distinct arguments. Each of these arguments is sufficient to overcome the rejection as it stands. That is, if the Examiner accepts any one of the Applicant's primary assertions, the rejection should be withdrawn.

In Section A, Applicant presents argument, declarations and prior art publications demonstrating that, contrary to the Examiner's understanding, a number of stabilized oligonucleotides were available for use in the invention in October of 1981.

In Section B Applicant explains that unmodified and unprotected oligonucleic acids can be, and have been, used *in vivo* according to the claimed method.

In Section C, Applicant will explain that the Examiner is mistaken when interpreting the Applicant's statement in 1984 regarding the Zamecnik and Stephenson references as an admission that unprotected and unmodified oligonucleotides were not useful for carrying out the invention.

In Section D, Applicant will explain that one of skill armed with the teachings of the subject application would not require undue experimentation to practice the invention as claimed.

In Section E, Applicant restates the legal argument previously submitted. Therein, Applicant explains that the Examiner's rejection is improper because it is not directed to the inventive principle of the claimed invention. Applicant respectfully urges the Examiner to carefully reconsider this legal argument which has been reframed in light of the most recent Office Action.

In Section F, Applicant concludes by addressing some minor issues relating to breadth rejections.

A. A VARIETY OF STABILIZED OLIGONUCLEOTIDES WERE AVAILABLE FOR USE IN THIS INVENTION PRIOR TO THE PRIORITY FILING DATE OF THE APPLICATION.

The Examiner has previously urged that at the time of filing of the parent application in October of 1981, there were no other stabilized oligonucleotides reported in the literature. Applicant has collected a number of articles which establish that there were several modified oligonucleotides available as of October 1981, each of which, according to the declarants, Drs. Ruth and Schwartz, would have been recognized by those of skill as suitable for use in the invention.

The Examiner is first asked to take note that the alkylphosphotriester DNA analogs described in the application were described in the literature in 1974 by Miller *et al.* (of record as reference A1). These analogs have a phosphate bearing four oxygens, one of which is substituted with an alkyl substituent.

Befort *et al.*(1974) describes a second chemically modified nucleic acid. Befort is already of record as reference A27. In Befort, the authors reported uptake of their stabilized RNA into fibroblasts and the subsequent inhibition of viral multiplication. The stabilized nucleic acid was a methylated RNA that complemented a portion of the viral genome.

In Tennant *et al.* (1974), the authors describe the *in vivo* effects of an alkylated homopolymer of ribonucleic acid on virally induced oncogenesis. Tennant is already of record as reference A47.

In Kunkel *et al.* (1981) (Exhibit 2 of the declarations), the authors report on a thio-substituted DNA molecule in which an oxygen of the phosphate is replaced by a sulfur. The authors clearly describe that previous work referenced in the paper taught them that the analog was readily incorporated into a polymer using a DNA polymerase and was nuclease resistant.

Finally, Miller *et al.* reported on the *in vivo* effects of a DNA analog in March 1981. This reference is already of record as A2. Attached to the declaration as Exhibit 1 is a true copy of the Medline abstract entry for this reference. The entry clearly identifies its publication date as March 1981, seven months before Applicant's filing date. The analog described by Miller in 1981 was an alkyl phosphonate. Alkyl phosphonates differ from the phosphotriesters of their earlier work by the direct attachment of the alkyl substituent to the phosphate. The Examiner is asked to review page 1879, second column, where a discussion of the intracellular half-lives of the phosphonates and the triesters are compared.

From the above discussion, it is clear that as of the priority filing date of the present application, those of skill would have understood the Applicant's reference to stabilized nucleic acid to have included more than the phosphotriester compounds that were provided as an example. The case law is clear. Patent applicants need not disclose what is already known to those in the art. *Paperless Accounting v. Bay Area Rapid Transit Sys.*, 231 USPQ 649 at 653 (Fed. Cir. 1986). Having disclosed both modified and unmodified nucleic acid as generically useful in the invention, having provided a specific example of stabilized nucleic acid, and having now presented evidence that other modified nucleic acids were available as of the priority filing date, Applicant submits that he has fully complied with the enablement requirement. Reconsideration of the rejection in view of the two declarations, exhibits and above remarks is requested.

B. OLIGO-DNAS CAN BE USED *IN VIVO* ACCORDING TO THE CLAIMED METHOD.

The Examiner has further rejected the claims under 35 USC §112, first paragraph, as only enabled for phosphotriesters. The Examiner is concerned that oligo-DNAs will not work under *in vivo* conditions because of a lack of stability. Although articulated under §112, first paragraph, this rejection is best considered as a combined §101/§112, first paragraph, utility rejection. This type of rejection concerns both the utility requirement under §101 and the "how to use" requirement of §112, first paragraph. The latter requirement relates to utility

because the "how to use" requirement of §112, first paragraph, incorporates as a matter of law the utility requirement of §101. *In re Ziegler*, 26 USPQ 2d 1601, 1603 (Fed. Cir. 1993).

When, as in the present case, utility or operability is doubted by the Examiner, applicants are permitted to submit declarations to overcome the rejection (see *In re Irons*, 144 USPQ 351 (CCPA 1965) and *Ex parte Aggarwal*, 23 USPQ 2d 1335 (BPA&I 1992). The first issue at hand, then, is whether oligo-DNAs can be used *in vivo* to suppress protein synthesis. As summarized below and described in the accompanying Rule 132 Declarations by Drs. Schwartz and Ruth, multiple modes of administration are suitable for delivering intact oligonucleotides to animals and isolated cells. Each of the following points is expressly supported by the attached declarations.

The Applicant would first direct the Examiner's attention to Michelson *et al.* and Wolff *et al.*(Exhibits 3 and 4, respectively) of the attached Rule 132 Declarations. Therein, Michelson described that ribonucleic acid survives up to a week inside the body of a rabbit. The article further indicates that the selected ribonucleic acid is biologically active for controlling neoplasms. In Wolff *et al.* the authors reported the expression of RNA after it was directly injected into the muscle tissue of a mouse. In the Michelson abstract, the authors report that no special delivery system was required to deliver either purified RNA or DNA and to permit its internalization by cells and subsequent expression. In Michelson, the authors report that three different genes were expressed by the mice.

The declarants also describe other publications reporting the injection of unmodified DNA for expressing genes under *in vivo* conditions. Reports involving the use of purified DNA are more numerous than of RNA. Exhibits 5 and 6 are illustrative reports of DNA expression of plasmids directly injected into animals. In Exhibit 5, Lin *et al.* (1990), the authors report on the expression of recombinant genes in heart tissue after the genes are simply injected into the heart of a living rat. The transfer media was simply phosphate buffered saline and sucrose. In Exhibit 6, Wolff *et al.* (1992), a second group reported similar results in mouse skeletal muscle using a gene encoding luciferase, and on page 368 (2nd

Col.), the authors report on the analogous results in a primate heart. According to the literature and declarants, the use of linear and circular DNA are equally useful.

In addition to expressing genes, unmodified antisense oligonucleotides have been demonstrated to downregulate specific gene expression in a variety of different tissues. The declarants describe several references teaching that naked, natural phosphodiester, antisense oligodeoxynucleotides are sufficiently stable to downregulate gene expression when directly injected into an animal. Examples include Exhibit 7, Phillips *et al.* (1994). Phillips *et al.* report on the successful downregulation of angiotensin and the AT_1 receptor by directly injecting an unmodified antisense DNA for reducing hypertension in mice. The DNA was merely injected into the mouse carotid artery using a saline solution.

Others have reported that antisense DNA will work when directly injected into the brain. For example, in Exhibit 8, Akabayashi *et al.* (1994), the authors added DNA to a saline solution and simply injected the solution into the brain to inhibit the expression of a neuropeptide. At page 56, 1st Col., the authors state that theirs is the third such report.

Finally, the Examiner's attention is directed to Exhibit 9, Hijiya *et al.* (1994). Hijiya *et al.* report on the use of an unmodified phosphodiester oligonucleotide for controlling the expression of a gene which is involved in skin cancer. The authors applied the antisense oligonucleotide via a subcutaneous route and used constant-infusion pumps to ensure that the oligonucleotide was adequately administered.

In view of the above academic articles teaching that antisense oligonucleotides are useful for downregulating specific protein expression under *in vivo* conditions, it is submitted that the Examiner's concerns about utility of the invention under §112, first paragraph, are fully addressed.

C. THE EXAMINER'S RELIANCE ON A STATEMENT IN THE FILE HISTORY REGARDING BREAKDOWN OF DNA IS NOT CONTROLLING OF PATENTABILITY.

In support of the rejection articulated under §112, first paragraph, the Examiner has cited a statement from a Disclosure Statement filed by Applicant's

previous attorney in 1984. The statement disclosed publications by Zamecnik and Stephenson and described their relevance to the pending claims. The Applicant's pending claims were limited at that time to stabilized oligonucleotides, and Applicant's attorney stated: "Finally, Zamecnik and Stephenson used an unprotected oligonucleotide, which would break down in vivo before having the desired effect."

The Examiner would have this phrase interpreted as an admission that unmodified DNA could not be used in the invention. Applicant respectfully suggests that the Examiner has read too much into this statement. The original specification clearly claimed both unmodified and modified oligonucleotides. In an attempt to obtain claims to the preferred embodiment, the Applicant limited his claims to stabilized oligonucleotides and noted the significance of this difference. This sentence was not an admission that the invention as presently claimed is useless, but is a simple statement inferring that there is going to be greater degradation with unprotected oligonucleotides. Moreover, the problem of degradation is trivial to solve. It is simply addressed by increasing the concentration of oligonucleotide in contact with the target cells.

The Examiner should also note that the sentence at issue was a side note to a more substantive argument distinguishing the pending claims from the prior art. Applicant's prior attorney clearly noted in the paragraph above that the Zamecnik and Stephenson references (hereinafter, Zamecnik) describe oligonucleotides that hybridize to the 5'-non-coding region of the target RNA. In addition, the Applicant stated that Zamecnik's oligonucleotides were non-specific, and apparently interfered with the circularization (rather than translation) of the viral RNA.

Even presuming that the sentence at issue properly raises a question regarding the possibility that phosphodiester oligodeoxyribonucleotides would be useless under *in vivo* conditions, the statement is far from an admission of a lack of utility. The Examiner's interpretation of the statement is clearly not the only possible interpretation of the sentence. Moreover, even if the statement were unambiguous, a poorly worded sentence should not be viewed as an error fatal to

patentability while prosecution is ongoing. Ambiguous and incorrect statements are occasionally made by patent applicants during prosecution. Basic elements of fairness should be considered and the Applicant should not be precluded from explaining any apparent ambiguity in statements made during prosecution.

Having explained the Applicant's actual intent of the sentence at issue, Applicant respectfully reminds the Examiner that Section B fully addresses the utility question raised by the Examiner. In Section B, it is explained that although oligo-DNAs may be unstable over a long period of time, the degree of stability does not prevent the practice of the invention *in vivo*. To maintain this rejection over the subject sentence is to unfairly limit the Applicant's claims to stabilized nucleic acid and that is merely a preferred embodiment.

D. UNDUE EXPERIMENTATION

Applicant, as noted in Section B, *supra*, traverses the Examiner's rejection on the grounds that the invention has been proven to be operable. Applicant's response focuses upon the issues raised by a hybrid rejection under §101 and §112. For completeness, the Applicant would like to address the rejection from a pure enablement perspective. Applicant would like to explain that it would not require undue experimentation to reduce this invention to practice.

As set forth above, the heart of the invention is the selection of oligonucleotides which bind to the coding region of the mRNA and to the use of appropriate length oligonucleotides. Once the inventive aspects of the oligonucleotides are recited, the practice of the invention is trivial, and given the level of skill in this art, the use of the invention to downregulate protein expression under *in vivo* conditions does not require undue experimentation. More specifically, Applicant submits that no undue experimentation is required when the practice of the invention merely asks one of skill to contact target tissue in a physiologically compatible buffer containing the oligonucleotides. It is an obvious extension of what was done to the cells in the test tubes and that is expressly taught.

E. THE EXAMINER HAS NOT CONSIDERED THE INVENTIVE PRINCIPLE OF THE INVENTION.

The Examiner has rejected the claims as allegedly not enabled for all oligonucleotides, and has required limitation to phosphotriester oligodeoxyribonucleotides. However, as Applicant has noted previously, the pending claims are not directed to phosphotriester oligonucleotides or other nucleic acid analogues, but to methods of specifically reducing expression of a targeted protein. Accordingly, the Examiner is respectfully urged to reconsider the rejection in light of the inventive principle of the claimed method.

The claimed method is the discovery that any oligonucleotides (including oligo-DNAs and stabilized oligonucleotides such as phosphotriesters) can access and bind to the coding region of a target mRNA thereby inhibiting expression of the protein encoded by the target mRNA.

Actual practice of this invention involves a number of steps, each of which can be carried out in a variety of ways. That is, the claimed method encompasses a multitude of physical embodiments. However, not every variation on the method is exemplified or taught. For example, the specification teaches that the nucleic acid sequence of a target mRNA can be determined by reference to the literature, by sequencing purified RNA, or from the amino acid of the corresponding protein, but does not recite sequence determination using *PCR*. However, no one would seriously assert that the application of the method to a target sequence determined by using PCR would not be covered by patentable claims. This is because the determination of the sequence of the target mRNA, although critical to some embodiments of the invention, is simply not the inventive principle. It is equally true that the specific structure of the oligonucleotide is not the inventive principle.

As noted in the previously submitted Amendment, there is clear decisional law that enablement issues for method claims, of the type now pending, must be confined to the patentable or inventive principles of the claimed method. Applicant believes it would be useful to briefly consider, for a second time, three cases discussed in the prior Amendment that speak to the issue of enablement and

the inventive principles of a claimed method. In *Application of Fuetterer*, 138 USPQ 217 (CCPA 1963), the applicant had discovered that the addition of a protein with an inorganic salt to the materials used to make tire tread increased the stopping ability of tires made from the materials. The Examiner in *Fuetterer* argued that the scope of the claims was too broad and the amount of experimentation required to successfully use undisclosed inorganic salts should require the applicant to restrict his claims to the disclosed salts. The CCPA reversed the breadth rejection, explaining that this invention was the combination of inorganic salts with the other elements of the claims. The fact that novel inorganic salts might be later developed did not preclude broad claims to the inventive combination.

Fuetterer was followed by *Application of Herschler*, 200 USPQ 711 (CCPA 1979). In *Herschler*, the applicant had discovered that dimethylsulfoxide (DMSO) was useful as a transdermal carrier for physiologically active steroids. The CCPA found that a priority application describing a single steroid (dexamethasone 21-phosphate) supported a claim to the genus of all steroids. Citing *Fuetterer*, the court explained that *Herschler*'s claims were not drawn to a novel steroid but to the method of administration of steroids. As long as the class of steroids could be expected to be carried across the skin by DMSO, the claim could encompass any steroid, known or unknown. As in *Fuetterer*, the CCPA reminded the Patent Office that the inventive principle was directed to a method of administration of steroids and that the specific steroid exemplified was not the point of patentability.

Fuetterer and *Herschler* illuminate the instant case. The inventive principle in *Fuetterer* was the combination of inorganic salt with other rubber stock components, not the use of a particular inorganic salt. The inventive principle in *Herschler* was a method for transdermal transport of all steroids, not the transport of dexamethasone 21-phosphate specifically. Similarly, the inventive principle of the instant invention is the targeting of mRNA coding regions by oligonucleotides, not targeting with phosphotriester oligonucleotides specifically.

Herschler provides guidance in identifying the inventive principle. There the court stated:

> The solicitor urges that the class of steroids is so large that a single example in the specification could not describe the varied members with their further varied properties. We disagree with this contention. Steroids, when considered as drugs, have a broad scope of physiological activity. On the other hand, steroids, *when considered as a class of compounds carried through a layer of skin by DMSO*, appear on this record to be chemically quite similar. (*Herschler* at 717; Italics added)

The invention in *Herschler* concerns the transdermal transport of steroids by DMSO; accordingly, steroids are considered as a class of compounds carried through skin and found to be presumptively similar in their ability to be carried. The instant invention concerns binding of oligonucleotides to mRNA; accordingly, oligonucleotides must be considered as a class of compounds capable of binding to mRNA. One of skill would understand that oligonucleotides, as a genus, are capable of binding RNA. Moreover, if provided with a novel oligonucleotide, one of skill could easily determine, with no undue experimentation, whether or not the novel oligonucleotide binds RNA. Following *Herschler* and *Feutter*, the requirement that the claims be limited to phosphotriester oligodeoxyribonucleotides must be withdrawn.

A third case on point is *In re Lange*, 209 USPQ 288 (CCPA 1981). In *Lange*, the court considered whether claims to a circuit breaker with electrodes consisting of a physical combination of metallic materials and non-metallic gas-emitting compounds were enabled by a grandparent application. The grandparent application did not teach how these materials could be cast together to form electrodes, but did teach how metallic materials and non-metallic gas-emitting compounds could be superimposed in layers. The CCPA found that the grandparent application was sufficient to enable claims directed to intimate mixing of the materials and compounds because the inventive principle did not reside in the preparation of electrodes but in the use of the electronegative nonmetallic gases. The court stated: "the method of forming the electrodes is not the inventive principle."

Analogously, in the instant invention, the discovery, synthesis or characterization of oligonucleotide analogues is not the inventive principle. Specific oligonucleotide analogues are not claimed and Applicant should not be required to enable their synthesis. Applicant is only required to enable the claimed *method of using* oligonucleotides, and has done so by specifying that the oligonucleotides are complementary to and able to bind a coding region of the target mRNA, are preferably about 14 to 23 bases in length, and are preferably stabilized. As noted above, once provided with this guidance, one of skill requires no undue experimentation to identify suitable oligonucleotides and practice the claimed method.

In accord with the case law, Applicant emphasizes that he does not claim the rights to specific phosphodiester oligodeoxyribonucleotides, phosphotriester oligodeoxyribonucleotides, or any other compositions of matter. Thus, like Herschler, who discovered that DMSO carries steroids across the skin and sought claims unlimited to specific steriod compositions, Applicant has taught that nucleic acids can access the coding region of mRNA and inhibit specific protein expression. In view of this teaching, Applicant seeks patent protection unlimited to the sequence or modification of nucleic acid.

F. MISCELLANEOUS COMMENTS

In retaining the rejection under §112, first paragraph, the Examiner has repeated the citations to MPEP §§706.03(n) and (z) made in the prior Office Action. In the prior amendment, Applicant provided a detailed argument explaining that these sections of the MPEP are not applicable to a breadth rejection as articulated by the Examiner. Applicant previously expressed a concern that the Examiner has either miscited these sections or has raised a rejection that is not clearly set forth. In addition, Applicant requested that if the Examiner maintained his rejection over §706.03(n), that he make specific reference to the offending language of the claims so that an appropriate amendment to the claims may be made.

Applicant notes that the present Office Action retains the citation to these MPEP sections but neither responds to the Applicant's arguments, beyond asserting that the arguments are "not convincing," nor provides clarifying language. Applicant continues to maintain that these MPEP sections do not provide a proper basis for this rejection, for the reasons set forth in the prior Amendment. Accordingly, Applicant requests that this rejection be withdrawn.

Applicant now believes the outstanding rejection has been fully addressed and overcome. Should the Examiner believe that prosecution can be expedited by a telephone interview, he is invited to call the undersigned attorney at the number provided below.

Respectfully submitted,

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Enclosures: Declaration of Dennis E. Schwartz
Declaration of Jerry L. Ruth
Exhibits 1-9